REMARKS

Applicants respectfully request reconsideration of the present application in view of the following remarks.

I. Status of the Claims

Claims 1-22, 24-30, 32-34 and 36-56 are pending in the application, with claims 1, 24-25, 32-33, 36 and 54-56 being the independent claims. Claims 23, 31 and 35 are canceled. Claims 1-22, 24-30, 32-34, 39 and 44-56 are withdrawn from consideration pursuant to a Restriction Requirement. Thus, claims 36-38 and 40-43 are currently under consideration.

II. The Rejection Under 35 U.S.C. § 102(e)

The Office Action, at page 2-3, rejects claims 36-38 and 40-43 under 35 U.S.C. § 102(e) as allegedly being anticipated by US Patent Application Publication No. US 2004/0229262 A1 to Franco *et al.* ("Franco"). Applicants respectfully traverse this ground of rejection.

A. Summary of the Claimed Invention

The presently claimed invention is directed to a method of treating major depression comprising administering a therapeutically effective amount of a pharmaceutical composition comprising BzATP to a subject suffering from major depression.

B. The Cited Reference Fails to Teach Each and Every Element of the Claimed Invention

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Franco discloses a polynucleotide encoding a novel human splice variant of the P2X7 purinoceptor named "HBMYP2X7v" (*see* paragraphs [0074] and [0116]). Nowhere does Franco

disclose a method of treating major depression comprising administering BzAtp to a subject in need thereof. In fact, the only disclosure with regard to BzATP in Franco may be found in paragraph [0677], which teaches that BzATP is a known agonist of P2X7 and may be used to *elucidate* the activity of HBMYP2X7v. Nowhere does Franco present evidence that HBMYP2X7v can indeed be activated by ATP and BzATP. Franco is even uncertain about the function of HBMYP2X7v, as it presents methods to assess whether HBMYP2X7v is a functional purinoceptor (*see* Example 4).

Although Franco provides the general teachings that modulators of HBMYP2X7v might have utility in the treatment of affective disorders, the reference does not even mention major depression among the neurodegenerative disease states, behavioral disorders and memory conditions which may be treated by modulators of HBMYP2X7v, let alone methods of treatment comprising administering BzATP (*see* paragraph [0135]).

Thus, Franco fails to anticipate the claimed invention.

C. The Cited Reference Teaches Away from the Claimed Invention

As stated above, Franco discloses a novel human splice variant of the P2X7 purinoceptor named "HBMYP2X7v". Figures 1A and 1B in Franco provide the polynucleotide sequence (SEQ ID NO: 1) and deduced amino acid sequence (SEQ ID NO: 2) of the variant HBMYP2X7v. The HBMYP2X7v variant lacks arginine at amino acid position 294, as illustrated by comparison with the complete amino acid sequence of the P2X7 receptor (*see* Exhibit A, attached herewith). Exhibit A discloses the complete amino acid sequence of P2X7. The red strikethrough sequence in Exhibit A represents the amino sequence deleted in HBMYP2X7v. Amino acid 294, which is essential for ATP response and is lacking in HBMYP2X7v, is indicated by a red circle.

Applicants submit that there is clear evidence in the literature that mutations in the purinoceptor P2X7 result in the loss of ATP response (*see* Adriouch *et al.*, *Cellular Immunology*

236 (2005): 72-77, attached herewith as Exhibit B). Thus, Exhibit B teaches that mutations in three conserved arginine residues at amino acid position 294, 307 and 316 in the extracellular loop of P2X7 result in the loss of ATP response, and specifically teaches that "The R294A mutant that was generated by site directed mutagenesis showed elevated cell surface expression but did not respond to ATP" (*see* Discussion at page 76). Thus, the evidence provided in Exhibit B establishes that the arginine at amino acid position 294 of P2X7 is essential for response to ATP and BzATP. Therefore, by providing a P2X7 variant which lacks an amino acid essential for response to BzATP, Franco teaches away from the present application, as the HBMYP2X7v variant would not be capable of responding to BzATP. And in fact, as stated above, Franco fails to provide any evidence that the HBMYP2X7v variant can respond to ATP and BzATP. Thus, Franco fails to anticipate the present invention.

C. The Cited Reference Fails to Provide Evidence that the HBMYP2X7v is Present in Affective Disorders

Franco also fails to demonstrate that the splice variant HBMYP2X7v is relevant in individuals suffering from major depression. Example 2 of Franco teaches that the splice variant HBMYP2X7v was isolated from hippocampal brain tissue of patients with Alzheimer's disease. However, Franco fails to demonstrate that the splice variant HBMYP2X7v can be isolated from or is present in hippocampal brain tissue of patients with affective disorders such as major depression. Consequently, Franco fails to teach that HBMYP2X7v is involved in affective disorders.

D. The Cited Reference Fails to Provide Evidence that an Agonist of P2X7R is Needed for the Treatment of Major Depression

Franco further fails to demonstrate that an agonist, not an antagonist, of P2X7R is required for the treatment of depression. In fact, the general knowledge at that time the invention of Franco was filed suggested that an antagonist of P2X7 is required for the treatment of affective disorders. For example:

WO 03/042191, submitted herewith as Exhibit C, discloses compounds that are potent antagonists and inhibitors of P2X7R (*see* for example page 1, lines 7-8), and teaches that such compounds with P2X7R antagonistic activity may be used to treat various diseases including depression (*see* page 36, line 24, and page 37, line 12).

Similarly, WO 03/042190, submitted herewith as Exhibit D, discloses compounds that are potent antagonists and inhibitors of P2X7R (*see* for example page 1, lines 7-8), and teaches that such compounds with P2X7R antagonistic activity may be used to treat various diseases including depression (*see* page 25, line 17, and page 26, line 4).

Further, WO 04/058270, submitted herewith as Exhibit E, discloses compounds that are potent antagonists and inhibitors of P2X7R (*see* for example page 1, lines 1-8), and teaches that such compounds with P2X7R antagonistic activity may be used to treat various diseases including depression (*see* page 33, line 1).

Finally, WO 04/058731, submitted herewith as Exhibit F, discloses compounds that are potent antagonists and inhibitors of P2X7R (*see* for example page 1, lines 1-8), and teaches that such compounds with P2X7R antagonistic activity may be used to treat various diseases including depression (*see* page 48, line 8).

Accordingly, at least for all the reasons stated above, Franco fails to explicitly or inherently anticipate the present invention. Thus, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

CONCLUSION

All of the stated grounds of rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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